

New Self-Expanding Transcatheter Valve for Off-Pump Transatrial Mitral Valve-In-Ring Implantation

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Key Words

Transcatheter · Mitral valve · Transatrial valve-in-ring implantation

Abstract

Objectives: To validate a self-expanding transcatheter valve for off-pump transatrial mitral valve-in-ring (VIR) implantation via a left thoracotomy. **Methods:** Mitral valve annuloplasty was performed via sternotomy during cardiopulmonary bypass on 9 pigs. After successful weaning from extracorporeal circulation, the custom-made, self-expanding transcatheter VIR device was deployed under fluoroscopic guidance within the annuloplasty ring via a left thoracotomy. Hemodynamic data before and after the implantation were recorded. Mitral annulus diameter and valve area were measured by echocardiography. Transvalvular and left-ventricular outflow-tract pressure gradient were measured invasively. **Results:** Eight successful implantations were performed. Implantation failed in 1 pig because of difficulty with technical delivery of the sheath. Mean transatrial procedure time was 12.6 ± 1.7 min. Hemodynamic status during transatrial implantation was stable, and differences were not statistically significant. Mean mitral annulus diameter and mean mitral orifice area were 2.32 ± 0.2 and 3.84 ± 0.55 cm², respectively. Mild regurgitation was detected in 7 animals

and moderate regurgitation in 1. Mean gradients were 6.1 ± 5.0 mm Hg across the device. Postmortem examination confirmed adequate positioning of devices within the annuloplasty ring. **Conclusions:** This custom-made transcatheter device allows for safe and reproducible off-pump transatrial mitral VIR implantations. Transatrial access is a promising route to facilitate VIR implantations. Our custom-made stent-valve may be suitable for VIR procedures.

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Introduction

Mitral valve repair is the preferred surgical therapy for mitral regurgitation. Annuloplasty rings are routinely used for restoring the mitral annular size and shape. The superiority of mitral valve repair over valve replacement has been shown [1, 2]. However, the durability of mitral valve repair is not satisfactory, especially in patients with ischemic regurgitation. Some centers report that at 6 months, up to 30% of patients suffer a recurrence of mitral valve regurgitation following valve repair [3–5]. Reoperation after 10 years is necessary in 5–10% of these

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Fig. 1. Custom-made, self-expanding, double-crowned VIR device (a) and its delivery system (b). c The 28-mm rigid annuloplasty ring was sewn to the mitral annulus under CPB (seen from the left side).

patients [2, 6]. Nevertheless, the high risk of repeat surgery, especially in the case of elderly patients, must be considered.

In the past decade, transcatheter valve replacement techniques have developed rapidly. Transfemoral and transapical transcatheter aortic valve implantation (TAVI) have shown very promising clinical results in selected patient populations. Although transcatheter mitral valve replacement has mostly remained at the stage of animal evaluation [7, 8], transcatheter mitral valve-in-valve (VIV) or valve-in-ring (VIR) implantation has slowly entered clinical practice. The VIR technique turns out to be a potential therapeutic technique for high-risk patients with mitral repair failure. Nevertheless, only isolated clinical cases and animal studies [9–13] have been reported due to the challenge of matching the stent and the ring. Moreover, only balloon-expanding TAVI devices like the Sapien or Melody valves [9, 10, 12, 14] have been used.

This study was designed to confirm the feasibility of transatrial transcatheter mitral VIR replacement via a left thoracotomy, without cardiopulmonary bypass (CPB) support and using a self-expanding dedicated nitinol device. We also wanted to evaluate its hemodynamic performance in an acute porcine model.

Materials and Methods

The Stent Valve

As described in our previous article [8], a 30-mm, self-expanding nitinol stent frame was designed, using 2 self-expanding nitinol Z-stents covered by an ultrathin polytetrafluoroethylene membrane. The stents were sutured together like 2 opposite crowns, creating a waist portion for the annular fixation. Next, a 30-mm-diameter Dacron tube was attached at the center of the fixation system, accommodating an inhouse-built tricuspid-tissue valve made from commercially available bovine pericardium (BalMedic,

Peking, P.R.C.; fig. 1a). All devices underwent thorough in vitro testing and were preserved in a glutaraldehyde solution prior to experimental in vivo use.

The Delivery System

Device delivery was performed using a self-constructed delivery system made from a 30-cm-long Teflon sheath and a blunt-tip pusher by modification of an 18-french introducer sheath (B. Braun Melsungen AG, Melsungen, Germany). The distal end of the sheath was dilated to a 30-french inner-lumen diameter by inflating a 10-mm balloon (Boston Scientific Corp., Watertown, Mass., USA). According to the stent's length, a 40-mm capsule was created [15]. The new valve device was then compressed with a commercial crimper and loaded into the capsule. The valve deployment in the appropriate position was performed with a pusher into the sheath and without balloon catheters. The folded valve measured 10 mm in diameter and 40 mm in length (fig. 1b).

Animal Preparation

The study was approved by the local Ethics Research Board. Animals received care in compliance with the 'the Guide for the Care and Use of Laboratory Animals' prepared by the Institute of Laboratory Animal Resources and published by the National Institute of Health (NIH publication 85–23, revised 1985).

Nine porcine experiments (the mean body weight of the pigs was 61.1 ± 5.2 kg) were performed in this acute study. After undergoing general anesthesia with tracheal intubation and mechanical ventilation (ketamine 22 mg/kg and atropine 0.8 mg/kg intramuscularly, thiopental 15 mg/kg intravenously for induction and isoflurane 2.5% for maintenance anesthesia), the right carotid artery and internal jugular vein were exposed and catheters were introduced to monitor the blood pressure and central venous pressure, and for blood sampling and infusion. The left carotid artery and the external jugular vein were prepared for cannulation for CPB. Arterial pressure, central venous pressure, oxygen saturation and electrocardiography were monitored continuously.

Annuloplasty Ring Implantation

After standard sternotomy and heparinization (100 IU/kg), the native mitral annular diameter and area were measured by epicardial echocardiography (Mindray, Shengzhen, China). CPB was established with cannulation of the left carotid artery and external jugular vein. After aortic cross-clamping, antegrade cardioplegia

was administered and the heart was arrested. Following opening of the left atrium, a rigid and closed 28-mm mitral annuloplasty ring (Edwards Lifesciences, Irvine, Calif., USA) was sutured into the mitral annulus (fig. 1c). After confirming mitral valve competence with saline injection, the left atrial access was closed again and the aortic cross-clamp removed. Once successful weaned from CPB, a repeat epicardial echocardiography was performed. Invasive transvalvular and left-ventricular outflow-tract (LVOT) pressure gradient were taken as baseline values and the sternum was subsequently closed with a 0# Maxon suture.

Transatrial Mitral Stent Valve Implantation

Via a fourth intercostal left-sided thoracotomy, a single purse-string suture was placed at the left atrium. The annuloplasty ring was identified under fluoroscopy. In parallel, the self-expanding, valved device was prepared and loaded onto the delivery system. Through a 1-cm incision, the left atrium was entered with the custom-made delivery system. Under fluoroscopic guidance, the annuloplasty ring was crossed and the device positioned in a 50/50 fashion within the ring. Without rapid ventricular pacing, the ventricular side of the stent was partially expanded by advancing the pusher. Next, the delivery system was gradually withdrawn until the anchoring portion of the stent was aligned with the ring. The delivery sheath was pulled continuously for atrial deployment of the device at the target (fig. 2a–f). Fluoroscopic guidance was used throughout the implantation.

Device function and hemodynamic impact were assessed with epicardial echocardiography and angiography at baseline and 30 min after implantation. The transprosthetic and trans-LVOT pressure gradient were measured invasively. Continuous hemodynamic measurements were taken for another hour and the animals were then electively sacrificed for postmortem examination and inspection of the device.

Statistical Analysis

Data were analyzed with SPSS v19 software for Windows. Variables are reported as mean \pm standard deviation (SD), and Student's *t* test was used for comparison.

Results

All animals underwent successful surgical placement of an annuloplasty ring. The mean cardiac arrest time and CPB time were 49.3 ± 11.7 and 74.1 ± 14.7 min, respectively. In 8 animals, successful transatrial mitral VIR implantation was performed. In 1 animal, positioning the device failed because the delivery sheath was withdrawn too fast which caused the device to migrate into the left ventricle. The mean procedure time defined from placing the purse-string to tightening the purse-string tightening was 12.6 ± 1.7 min. Mean flow time was 6.3 ± 3.2 min. Hemodynamic data before and after transatrial valve deployment appear in table 1.

The mean diameter of the native mitral annulus was 2.58 ± 0.22 cm, and the mean mitral valve area was $4.58 \pm$

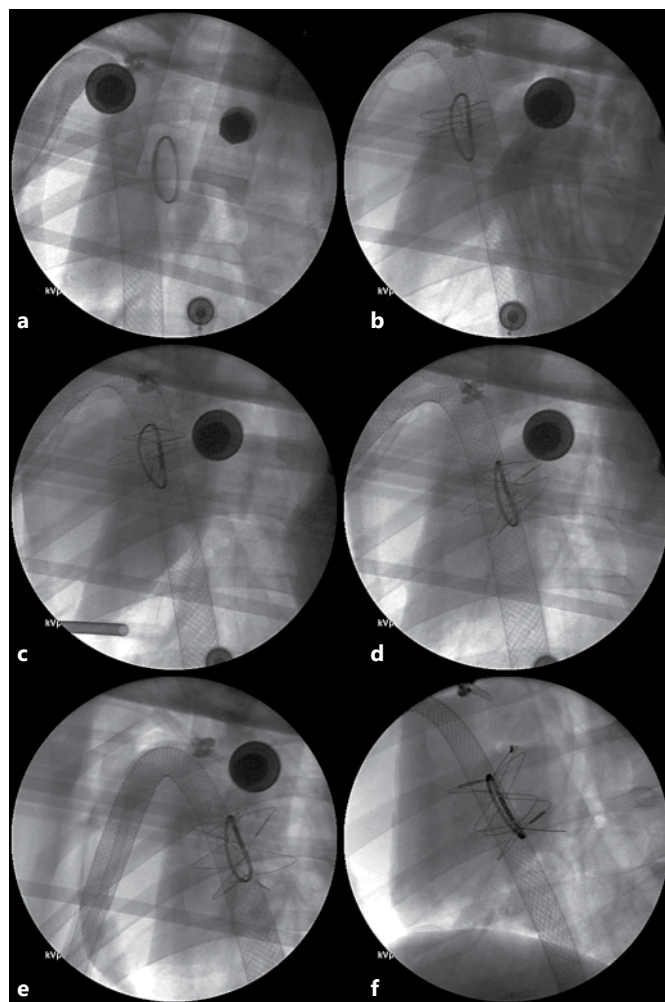


Fig. 2. **a** The mitral annuloplasty ring is radiopaque. **b** The self-expanding device is delivered across the ring via release of the ventricular side first, by advancing the delivery pusher (**c**). **d, e** Under gentle pull-back, the delivery sheath is pulled to continuously deploy the atrial side. **f** Precise device implantation is achieved at target position within the ring.

0.29 cm^2 on echocardiography evaluation. Comparatively, the mean diameter and mean functional area of the self-expanding device after implantation were 2.32 ± 0.2 and $3.84 \pm 0.55 \text{ cm}^2$, respectively. No statistical difference existed in mitral diameter before and after implantation. However, the functional area before and after the procedure were significantly different (i.e. $p = 0.012$ and $p < 0.05$). Of the 8 successful implants, all valve leaflets had normal mobility and function (fig. 3a, b). Trace or mild central regurgitation was detected in 7 valves; in 1, a moderate central regurgitation was shown due to interaction with the Dacron device cover. No paravalvular leak between the stent frame and the annuloplasty ring was observed (table 1).

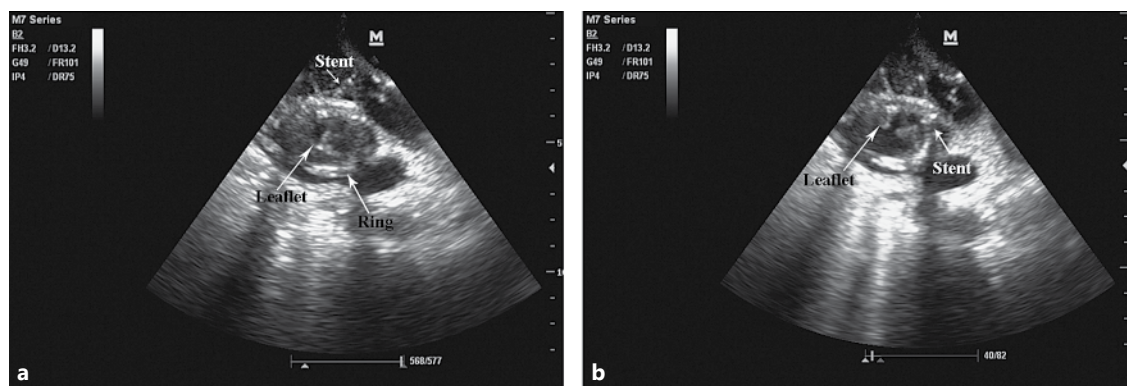


Fig. 3. Epicardial echocardiography revealed excellent device function with complete leaflet opening (a) and closing (b).

Table 1. Procedural data and hemodynamic and implanted stent valve function

No.	Weight, kg	HR ^a , bpm		BP ^a , mm Hg		CVP ^a , mm Hg		Valve diameter ^a , cm		Valve area, cm ²		Arrest time, min	CPB time, min	Transapical time, min	Across valve, mm Hg	Across LVOT, mm Hg
		pre	post	pre	post	pre	post	native	stent	native	stent					
1	60	106	135	100/77	91/50	10	8	2.52	2.50	4.70	4.10	35	50	10	7	3
2	63	114	90	83/47	88/55	8	7	2.43	2.40	4.63	4.02	50	65	12	3	7
3	54	104	97	83/54	87/72	7	8	2.60	2.10	4.21	3.81	35	65	15	4	2
4	70	101	113	86/50	83/43	9	6	2.58	2.16	4.20	3.62	60	90	13	4	1
5	67	92	n.a.	115/63	n.a.	12	n.a.	2.61	n.a.	6.01	n.a.	43	63	15	n.a.	n.a.
6	57	100	96	111/77	103/68	11	7	3.10	2.00	4.85	2.59	65	90	12	18	6
7	61	114	103	93/66	94/37	7	6	2.45	2.50	4.91	4.24	60	85	13	3	4
8	56	86	97	90/56	95/52	8	7	2.50	2.40	4.37	4.11	39	70	11	5	5
9	62	90	100	103/62	98/56	7	9	2.47	2.52	4.80	4.21	57	89	12	5	10
Mean	61.1	101.9	103.9	93.6/61.1	92.4/54.1	8.4	7.3	2.58	2.32	4.58	3.84	49.3	74.1	12.6	6.1	4.8
SD	5.2	10.1	14.2	10.2/11.5	6.5/11.7	1.5	1.0	0.22	0.21	0.29	0.55	11.7	14.7	1.7	5.0	2.9

Across LVOT = Gradient across LVOT; Across valve = gradient across valve; BP = blood pressure; CVP = central venous pressure; HR = heart rate; n.a. = not available (due to failed implantation); post = after VIR placement; pre = before VIR placement; SD = standard deviation.

^a Differences between hemodynamics before and after the VIR implantation were not statistically significant.

Mean pressure gradient across the self-expanding device was 6.1 ± 5.0 mm Hg. The corresponding gradients across the LVOT were 4.8 ± 3.0 mm Hg (table 1).

Postmortem examinations confirmed the precise device positioning within the annuloplasty rings in 8 animals with no signs of LVOT obstruction (fig. 4a, b).

Discussion

Transcatheter replacement of the native mitral valve has been reported previously [16]. However, due to the complex anatomic structure of the mitral valve apparatus

and the absence of a reliable 'landing zone' [10], most results are from animal experiments only [7]. VIV and VIR implantation techniques into the mitral position haven been clinically introduced more successfully. Avoiding reoperation and standardizing the 'landing zone' of previously placed bioprosthesis or annuloplasty rings support the drive for dedicated VIV and VIR device development. The in situ bioprosthesis as well as the mitral annuloplasty ring provide distinctive fluoroscopic landmarks [17]. The congruence between valve and prosthesis/annulus is a key factor for avoiding paravalvular regurgitation [18]. In contrast to the straightforward VIV implantations into a circular mitral valve bioprosthesis

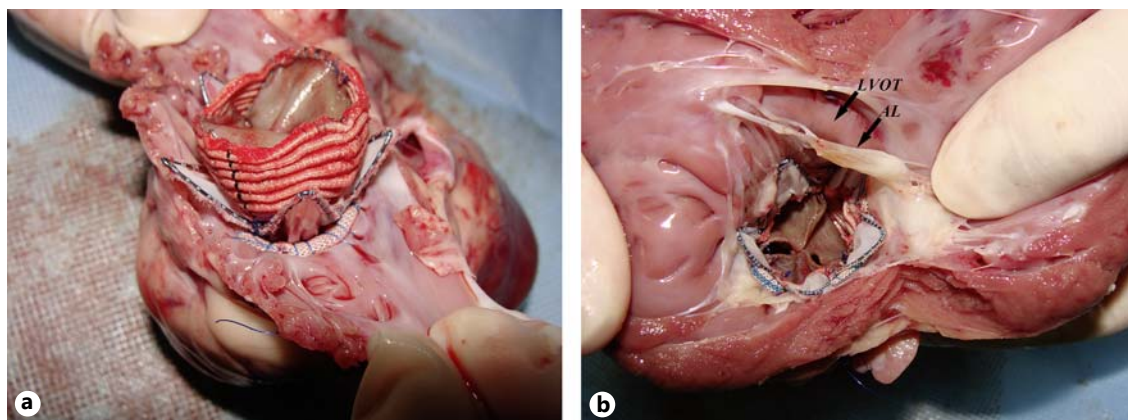


Fig. 4. Postmortem examination revealed accurate delivery without LVOT obstruction. **a** Left atrial side. **b** Left ventricular side.

[19–21], the ‘D’ shaped mitral valve annuloplasty ring presents an important challenge for TAVI devices. Malapposition and noncircularity might lead to leaflet malcoaptation, resulting in regurgitation and early degeneration of the device. The overall experience of VIR is mostly limited to isolated clinical case reports, small series and animal studies [10, 14, 22–24]. Descoutures et al. [10] reported preliminary multicenter results of 17 cases, and that VIR may provide short-term clinical and hemodynamic improvement.

There are 3 accesses that are favorable for transcatheter VIR implantation, i.e. transapical, transseptal and transatrial. The transapical access has become a routine approach due to its safety, reproducibility and low complication rate. Allowance for the implantation of large-size devices and a short access to both the mitral and the aortic valve are further advantages [17]. However, it does have some shortcomings. On the one hand, the mitral valve apparatus interferes with the delivery system while crossing the mitral valve [7] and on the other, a surgical cutdown and manipulation of the left ventricular apex are necessary. The transseptal approach is a frequently used percutaneous technique [25]. However, with this access, there is a clear need for advanced interventional skills and associated learning [10]. Despite being an antegrade access to the mitral valve, due to the long wires and catheters, device positioning and delivery is less precise [11]. The other antegrade approach is the transatrial access that offers distinct advantages for mitral implants, namely (1) the ease of antegrade valve crossing, (2) atrial access with eased bleeding control, (3) a more linear and coaxial angle to the mitral valve [24] and (4) a short working distance with easier stabilization for device de-

ployment [10]. Our study confirms the eased mitral valve crossing using the transatrial rather than the transapical access [13].

In this study, we successfully performed transatrial mitral VIR implantations using a custom-made, dedicated VIR device. In 8 of the 9 porcine experiments, stable hemodynamics were achieved throughout the procedure. This finding validates the feasibility of off-pump transatrial mitral VIR implantations via a left thoracotomy with the use of our self-expanding device.

However, we did detect a moderate central regurgitation in 1 case. Postmortem examination found that the soft Dacron tube was partially deformed and the resulting interaction with the device leaflet led to malcoaptation of the cusps and subsequent regurgitation. In addition, device iterations are necessary to improve the ring device interaction.

In our study, the transvalvular gradient pressures were suboptimal because of the amount of material within the stent. As described above, a Dacron tube for accommodating a valve was an extra component in our stent. Moreover, this tube was soft and might have become partly deformed while the blood flowed through it. All of these factors resulted in higher transvalvular gradient pressures. The next generation of our stent will be designed with a rigid tube, which will replace the soft tube to support the valve, avoiding an excess of extra components in the direction of the blood flow. The diameter of our stent valve remained constant. We could not choose the proper stent valve according to annulus diameter. We have taken this into consideration. The next generation of stent valve will be designed on the basis of a different annulus diameter, thus providing a bet-

ter foundation of its usefulness in human experiments in future.

So far, the balloon-expandable transcatheter heart valve is the only available valve used in reports on mitral VIV or VIR procedures [10]. There are several disadvantages to be mentioned when comparing balloon-expandable to self-expanding devices: (1) the need for rapid ventricular pacing, (2) malpositioning, i.e. either too atrial or too ventricular [10, 25] and (3) the effective valve orifice after implantation is much lower than the area of native mitral valve [10, 25]. Based on our previous [13] and current studies, we can say that the self-expanding, double-crown device achieves a self-centering and self-aligning anchoring into the annuloplasty ring. Due to the supra-annular implantation, our device resulted in a larger effective orifice after implantation. The functional area after the implantation was $3.84 \pm 0.55 \text{ cm}^2$, approximating the native valve area of $4.58 \pm 0.29 \text{ cm}^2$. These results were also in line with our previously published results [13].

There are many reasons for the recurrence of mitral valve regurgitation following valve repair. Our custom-made stent valve expands completely to get an ideal effectiveness for patients with a flexible valve, whose recurrence of mitral valve regurgitation may be caused by fracture of the manual chordae tendineae or ischemia. However, for the recurrence of mitral valve regurgitation caused by rheumatic heart disease or degeneration of the valve, the presence of calcific or rigid valve not only prob-

ably leads to our custom-made stent valve expanding uncompletely, deforming or displacement, but also affects the delivery of the stent. Balloon dilatation should be applied several times before mitral VIR implantations to get a large effective orifice area.

It is evident that there are differences between a dysfunctional and a normal mitral valve; we have taken this into account for our next experiment. A model of a dysfunctional mitral valve will be made to test our self-expanding VIR device for its accommodation in treatment for the recurrence of mitral valve regurgitation following valve repair.

In conclusion, this study demonstrated the feasibility of transatrial mitral VIR implantation via a left thoracotomy, without extracorporeal circulation and using a dedicated, double-crowned, self-expanding VIR device. The larger effective orifice area and the suprannular fixations are major advantages over the currently used balloon-expandable device.

Acknowledgement

This work was supported by National Natural Science Funding of China (81070264).

Conflict of Interest

The authors declare that there are no conflicts of interest.

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